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Harvesting the Neural Gene Therapy Fruit

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Introduction

This is a critical time for the field of gene therapy. There have been spectacular recent successes (e.g., in the treatment of SCID and hemophilia B), but public wariness and government scrutiny have escalated following Jesse Gelsinger's death in the University of Pennsylvania OTC trial in late 1999. Although it is too early to predict the final effects of these events on government oversight of gene therapy, there has been a notable slowdown in the movement of gene therapy applications from the bench to the clinic. Gene therapy-related Investigational New Drug (IND) applications to the U.S. Food and Drug Administration (FDA) have decreased by half during the past year, and amendments to current INDs have almost tripled. Advances in the basic science underlying gene therapy are occurring at a breathtaking rate, but there appears to be an ever-thickening barrier to translating these advances to the clinic.

One area in which gene therapy holds great promise is in the treatment of neurological disease. There is a wide range of neurodegenerative disorders, including Parkinson's disease and Alzheimer's disease, for which no entirely effective therapies currently exist. Successes in treating a variety of neurological diseases in animal models are spurring investigators to consider clinical trials in humans with these diseases. However, recent events have led these investigators to hesitate. Where should the line between appropriate caution and the urgent need for developing treatments be drawn?

To address this and other questions, the National Institute of Neurological Disease and Stroke (NINDS) sponsored a two-day workshop on October 23 and 24, 2000, in Rockville, Maryland. The goal of the meeting was to assess the state of preclinical gene therapy science for both Parkinson's disease (PD) and the group of diseases collectively known as lysosomal storage disorders (LSDs). The meeting was organized by Robert Finkelstein and Robert Baughman of NINDS in conjunction with Inder Verma and Fred H. Gage from the Salk Institute for Biological Studies (see Table 1 for the complete list of participants). Experts in PD or LSD from basic and clinical science in academia and industry were brought together to assess the state of their respective area of study and to outline the remaining questions and/or needs before moving into clinical trials. In addition, regulatory officials from the NIH and the FDA were present, as well as representatives from several voluntary patient advocacy groups. Another goal of the meeting was to encourage new collaborations and information exchange that could help push neurological gene therapy farther down the translational pathway. The following is both a report on the meeting discussions and a review of the many difficult issues that surfaced in the course of what all agreed to be a most productive and interesting gathering.

Neurodegenerative Diseases and Gene Therapy: Common Problems

In many respects, the unresolved issues holding back trials of gene therapy for neurological disorders are the same as those facing any gene therapy application: What gene is appropriate for transfer? Which vector will be most effective? What route of administration is best? How do we monitor the expression of a transferred gene? Which animal model is most appropriate to the human disease we want to treat? And what are the outcome measures that tell us this intervention is working? These questions are fundamental to any translational gene therapy undertaking.

However, the nervous system, particularly the CNS, poses additional challenges. Gerald Fischbach, NINDS Director, pointed out in his opening remarks that "In the brain, geography is everything," and that it is therefore critical to get any gene introduced into exactly the right place. Furthermore, although many of the morphological and chemical effects of neurodegenerative diseases are known, the precise mechanisms underlying those defects are not yet well understood. Although advances are being made, the precise immune status of the brain remains uncertain. Finally, because of its complexity, the CNS can react in unanticipated ways to any kind of invasive procedure.

Nevertheless, tremendous strides in developing possible treatments have been made in animal models of human neurodegenerative diseases. The critical question is how to determine, for a specific disorder, when sufficient animal data have been generated to justify moving into the clinic. The two disorders considered at the meeting, PD and LSDs, highlight the problems involved in making this decision.

Parkinson's Disease: The Ripest Fruit?

Current Status

A devastating and common disease, PD is linked to the gradual loss of dopaminergic neurons in the brain stem and their terminals in the striatum, although other subpopulations of neurons may also be involved. In his overview of the disease, Un Kang of the University of Chicago outlined the clinical features that lead to diagnosis of PD and the current treatment options aimed at slowing dopaminergic loss. Of all the treatments tried to date, oral

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